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An Efficient Transformation from Benzyl or Allyl Halides to Aryl and Alkenyl Nitriles

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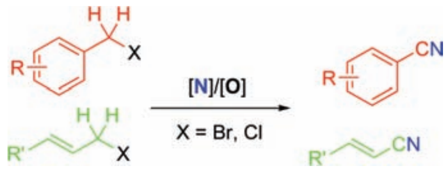
ABSTRACT



A novel approach to aryl or alkenyl nitriles from benzyl and allyl halides has been developed. A tandem TBAB-catalyzed substitution and the subsequent novel oxidative rearrangement are involved in this transformation. To the best of our knowledge, this is the first transformation from allyl halides to alkenyl nitriles. The broad reaction scope and the mild conditions may make these methods of use in organic synthesis.

The value of aryl and alkenyl nitriles in chemistry and biology as unique structural units and versatile building blocks in organic synthesis for natural products, pharmaceuticals, agricultural chemicals, and dyes has inspired the invention of numerous methods for their preparation.[1] To date, many elegant methods have been developed.[2–6] However, the transformation from simple and readily available organic halides is still limited. To the best of our knowledge, only a few approaches from benzyl halides to aryl nitriles have been reported.[7] The conversion from allyl halides to alkenyl nitriles has not been disclosed.

Recently, we reported a direct transformation of methyl arenes to aryl nitriles at room temperature (a, Scheme 1).[8] However, there still are some flaws in our method: (1) a *p*-heteroatom on the aromatic ring is required for the transformation, which extremely limited the substrate scope; (2) excess amounts of NaN_3 (4.0 equiv) and the oxidant (phenyliodonium diacetate, PIDA, 3.2 equiv) were employed to realize the transformation; (3) alkenyl methanes cannot

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Scheme 1. Strategies for Preparation of Aryl and Alkenyl Nitriles

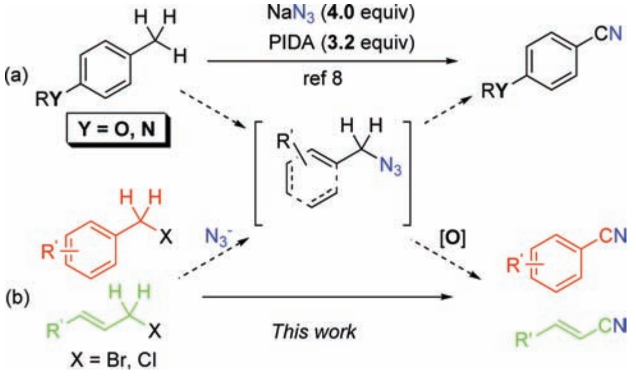
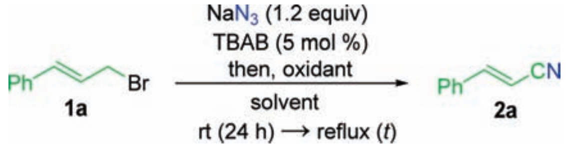


Table 1. The Direct Approach to Alkenyl Nitrile **2a** from Allyl Bromide **1a**[a]



entry	oxidant (equiv)	solvent	time (h)	yield of **2a**[b] (%)
1[c]	DDQ (2.0)	CH_2ClCH_2Cl	12	3
2	PIDA (2.0)	CH_3CN	6	8
3	CAN (2.0)	CH_3CN	6	0
4	DDQ (1.3)	CH_3CN	2	70
5	BQ (2.0)	CH_2ClCH_2Cl	2	0
6	**DDQ (1.3)**	CH_2ClCH_2C	**0.5**	**84 (81)**
7[d]	DDQ (1.3)	CH_2ClCH_2Cl	2	80
8[e]	DDQ (1.3)	CH_2ClCH_2Cl	2	0
9[f]	DDQ (1.3)	dioxane	2	65
10[f]	DDQ (1.3)	CH_3NO_2	2	42
11	DDQ (1.3)	ethyl acetate	2	37
12[f]	DDQ (1.3)	DMSO	2	22
13[f]	DDQ (1.3)	DMF	2	16

[a] Reaction conditions: **1a** (0.5 mmol), NaN$_3$ (0.6 mmol), TBAB (0.025 mmol) in dry solvent (2 mL), stirred at 25 °C under N$_2$ for 24 h; oxidant was then added, and the mixture was heated to reflux. [b] GC yield using *n*-dodecane as internal standard; the number in the parentheses is the isolated yield. [c] The oxidant was added together with the other reagents at the first step and then refluxed for 12 h. [d] 18-Crown-6 (0.05 equiv) was used instead of TBAB. [e] The reaction was carried out in the absence of TBAB. [f] The 2nd step was carried out at 100 °C.

be transformed to alkenyl nitriles under those conditions. Our continued efforts in the development of efficient nitriles synthesis promoted us to explore a broad-spectrum approach to nitriles. In our reported method,[8] it was demonstrated that benzyl azide is the key intermediate, which undergoes a novel oxidative rearrangement to afford aryl nitrile. We envisioned that benzyl and allyl azides, which could be easily prepared from simple and readily available organic halides, could be the potential precursors for the corresponding aryl and alkenyl nitriles through a proper oxidation (b, Scheme 1). Herein, we demonstrate a novel TBAB (tetra-*n*-butylammonium bromide)-catalyzed tandem substitution and the subsequent oxidative rearrangement approach to aryl and alkenyl nitriles from benzyl and allyl halides, respectively (b, Scheme 1).

Our approach was initiated using cinnamyl bromide **1a** as the electrophile (Table 1). As we expected, (*E*)-3-phenyl-2-propenenitrile **(2a)** was detected in 3% yield when **1a** was treated with sodium azide in the presence of DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) and a catalytic amount of TBAB refluxed in DCE (1,2-dichloroethane) for 12 h (entry 1, Table 1). Considering that the presence of an oxidant would probably affect the substitution step forming the allyl azide intermediate, we tried to add the oxidant subsequently. Gratifyingly, when DDQ was simply added after the reaction mixture had stirred at room temperature

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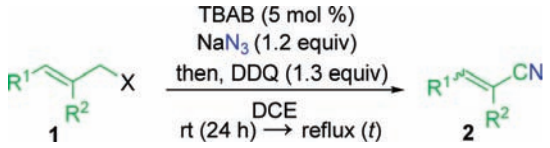
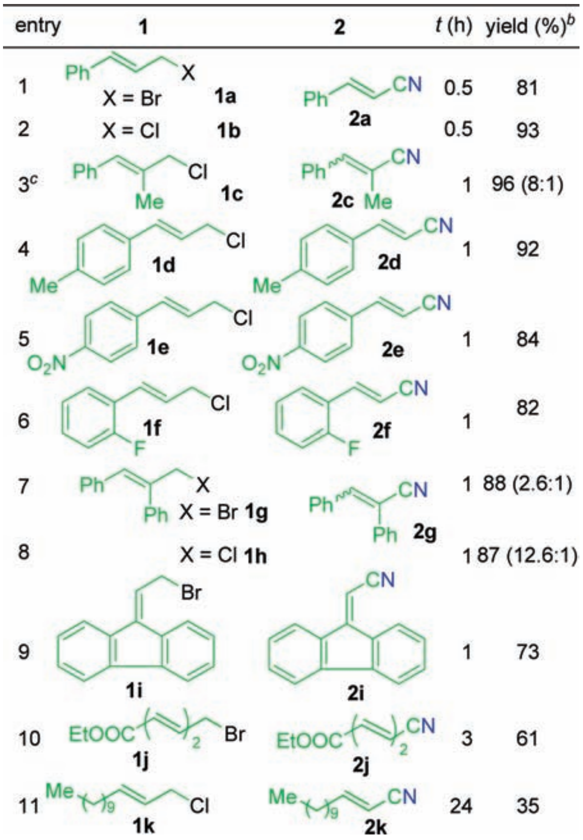
Table 2. Synthesis of Alkenyl Nitrile from Allyl Halides[a]

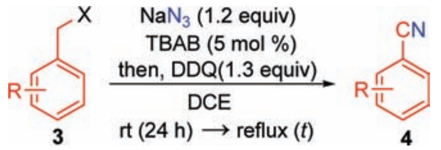


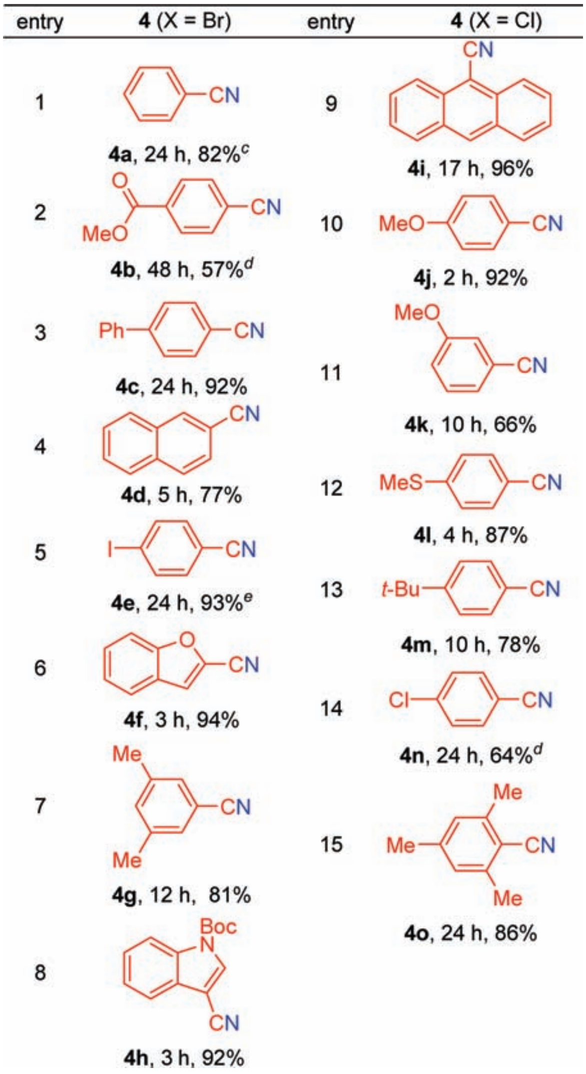


entry	1	2	t (h)	yield (%)[b]
1	X = Br **1a**	**2a**	0.5	81
2	X = Cl **1b**		0.5	93
3[c]	**1c**	**2c**	1	96 (8:1)
4	**1d**	**2d**	1	92
5	**1e**	**2e**	1	84
6	**1f**	**2f**	1	82
7	X = Br **1g**	**2g**	1	88 (2.6:1)
8	X = Cl **1h**		1	87 (12.6:1)
9	**1i**	**2i**	1	73
10	**1j**	**2j**	3	61
11	**1k**	**2k**	24	35

[a] Reaction conditions: **1** (0.5 mmol), NaN_3 (0.6 mmol), TBAB (0.025 mmol) in dry solvent (2 mL), stirred at 25 °C under N_2 for 24 h; then the oxidant was added and the mixture was heated to reflux. [b] Isolated yield; the number in parentheses is the ratio of the *E*- to *Z*-isomers of the product determined by ^1H NMR or GC (see the Supporting Information).

Table 3. Synthesis of Aryl Nitrile from Benzyl Halides[a,b]





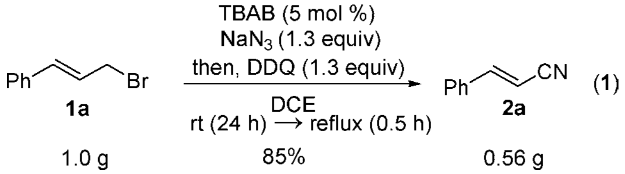
entry	4 (X = Br)	entry	4 (X = Cl)
1	**4a**, 24 h, 82%[c]	9	**4i**, 17 h, 96%
2	**4b**, 48 h, 57%[d]	10	**4j**, 2 h, 92%
3	**4c**, 24 h, 92%	11	**4k**, 10 h, 66%
4	**4d**, 5 h, 77%	12	**4l**, 4 h, 87%
5	**4e**, 24 h, 93%[e]	13	**4m**, 10 h, 78%
6	**4f**, 3 h, 94%	14	**4n**, 24 h, 64%[d]
7	**4g**, 12 h, 81%	15	**4o**, 24 h, 86%
8	**4h**, 3 h, 92%		

[a] Reaction conditions: **3** (0.5 mmol), NaN_3 (0.6 mmol), TBAB (0.025 mmol) in dry solvent (2 mL), stirred at 25 °C under N_2 for 24 h; DDQ (0.75 mmol) was then added, and the mixture was heated to reflux. [b] Isolated yield. [c] GC yield using *n*-dodecane as internal standard. [d] DDQ (1.8 equiv) was used. [e] DDQ (1.5 equiv) was used.

for 24 h, followed by refluxing for 0.5 h, **2a** was isolated in 81% yield (entry 6). Other oxidants, such as PIDA, CAN (ceric ammonium nitrate), or BQ (benzoquinone), exhibited lower efficiency than DDQ (cf. entries 2−5). In some cases, a trace of cinnamaldehyde was detected as byproduct. However, no product **2a** was obtained in the absence of TBAB (entry 8). Notably, 18-crown-6 worked equally well as phase-transfer catalyst (entry 7). Other solvents, such as 1,4-dioxane, acetonitrile, CH_3NO_2, ethyl acetate, DMF, or DMSO, gave **2a** in lower yield (entries 9−13, Table 1).

After confirming the optimum reaction conditions, we then probed the scope of this novel transformation (Table 2). A range of allyl chlorides and bromides proceeded efficiently to give the corresponding alkenyl nitriles in moderate to excellent yields. There is no significant effect on yield between allyl bromides and chlorides as the starting materials (cf. entries 1 and 2, 7 and 8). Moreover, the results in Table 2 demonstrate that the reaction has a high degree of functional-group tolerance. Aryl or alkenyl substitutents are well-tolerated (entries 1−10). Even alkyl-substituted allyl chlorides such as **1k** underwent this conversion to generate **2k**, but in lower yield (35%, entry 11). In addition, when allyl halides containing trisubstituted carbon−carbon double bond were employed as the substrates, such as (*E*)-**1c**, (*E*)-**1g**, and (*E*)-**1h**, the corresponding alkenenitriles were preferentially formed the *E*-isomers (entries 3, 7, and 8).

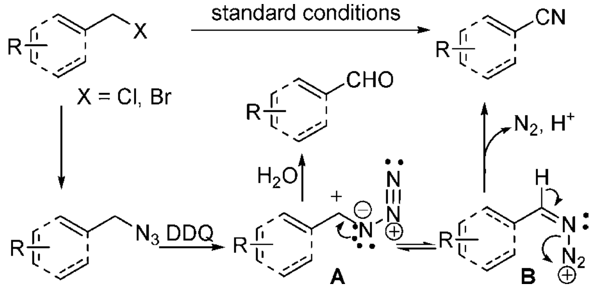
As shown in Table 3, this procedure worked well with a wide range of aryl halides **3** and gave the corresponding aryl nitriles in moderate to excellent yields. High yields were achieved with substrates containing methyl (**4g**, **4o**), *tert*-butyl (**4m**), phenyl (**4c**), and iodo (**4e**) functional groups. 2-Bromomethylnaphthalene and 10-chloromethylanthracene gave the corresponding nitriles in 77% and 96% yields, respectively (**4d**, **4i**). Moreover, heteroaryl bromomethanes such as **3f** and **3h** performed well, producing corresponding nitriles **4f** and **4h** in 94% and 92% yields, respectively (Table 3). Notably, 4-methylthiobenzyl chloride (**3l**) was converted to nitrile **4l** in good yield (87%) without further oxidation. Moderate yields were observed for the substrates with electron-withdrawing groups (**4b**, **4n**).



To investigate the practical application of this transformation in organic synthesis, gram-scale reaction of **1a** was conducted (eq 1). Interestingly, **2a** was produced in 85% yield without any decrease compared to the small-scale reaction (cf. eq 1 and entry 1, Table 2).

The plausible mechanism of this transformation is proposed in Scheme 2. The initial substitution reaction of benzyl and allyl halides produce benzyl and allyl azides, which are oxidized by DDQ[9] to form benzyl and allyl cations **A**, respectively. Then the cations **A** undergo Schmidt-type rearrangement[10] to afford the product aryl and alkenyl nitriles. During this procedure, the intermediates **A** could be attacked by water, leading to aldehydes,[11] which were observed in some cases by GC.

Scheme 2. Proposed Mechanism for the Cascade Transformation



In summary, we have developed a novel TBAB catalyzed tandem approach to aryl and alkenyl nitriles. To the best of our knowledge, this is the first transformation from allyl halides to allkenenitriles. This opens the door not only for other types of transformations for the synthesis of aryl and alkenyl nitriles with these simple and readily available substrates but also for the novel DDQ-oxidized rearrangement mechanism. The broad reaction scope, the readily available substrates, and the mild conditions may make these methods of significance in organic synthesis. Further studies on the mechanism and synthetic applications are ongoing in our group.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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